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10/005,216	12/04/2001	Keith D. Allen	R-881	6807

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EXAMINER
BERTOGLIO, VALARIE E

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 02/24/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

PTO-90C (Rev. 10/03)

Office Action Summary	Application No.	Applicant(s)	
	10/005,216	ALLEN, KEITH D.	
	Examiner	Art Unit	
	Valarie Bertoglio	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *10 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23,24,26 and 28-35* is/are pending in the application.

4a) Of the above claim(s) *34 and 35* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,24,26 and 28-33* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *34 and 35* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 July 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/10/2004 has been entered.

Election/Restrictions

Newly submitted claims 34 and 35 are directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: The originally elected invention included a transgenic knockout mouse, methods of making the mouse and a method of using the mouse as a phenotypic model to screen for agents that modulate a phenotype of the knockout animal (see original claim 18). It appears that newly added claims correlate most closely to original claim 10, which is patentably distinct as set forth in the restriction requirement mailed 10/24/2003. The method claim 25 of the previously pending claim set has been cancelled and is distinct from the newly added claims 34 and 35.

The knockout mouse and the methods of the newly added claims are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case the knockout mouse can be used in various distinct and different methods that require different method steps and different technical considerations. As claimed in the original, cancelled claims the mouse

can be used as a phenotypic model to screen for agents that modulate a phenotype of the knockout animal (see previously pending claims 18 and 25). This method differs from the method of the newly proposed claims that are directed to methods of using the knockout mouse as a control to identify modulators of TRP6 activity or expression in a wild-type mouse. Furthermore, the newly claimed methods would require a search that was not required by the original invention previously under examination. The newly claimed methods present new issues of consideration that were not of issue in the elected invention. As such, it would require an undue burden on the part of the office to examine the newly proposed claims as part of the instant application.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution on the merits. Accordingly, claims 34 and 35 are withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of In

re Ochiai, In re Brouwer and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.** Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Claims 23,24 and 26 have been amended. Claims 25 and 27 have been cancelled. Claims 28-35 have been added. Claims 34 and 35 are withdrawn from consideration as being drawn to a non-elected invention. Claims 23,24,26 and 28-35 are pending. Claims 23,24,26 and 28-33 are under consideration in the instant office action.

Claim Rejections - 35 USC § 101/112

Utility

Definitions:
[from REVISED INTERIM UTILITY GUIDELINES TRAINING MATERIALS; repeated from http://www.uspto.gov/web/menu/utility.pdf]

"Specific Utility" - A utility that is specific to the subject matter claimed. This contrasts with a general utility that would be applicable to the broad class of the invention. For example, a claim to a polynucleotide whose use is disclosed simply as a "gene probe" or "chromosome marker" would not be considered to be specific in the absence of a disclosure of a specific DNA target. Similarly, a general statement of diagnostic utility, such as diagnosing an unspecified disease, would ordinarily be insufficient absent a disclosure of what condition can be diagnosed.

"Substantial utility" - a utility that defines a "real world" use. Utilities that require or constitute carrying out further research to identify or reasonably confirm a "real world" context of use are not substantial utilities. For example, both a therapeutic method of treating a known or newly discovered disease and an assay method for identifying compounds that themselves have a "substantial utility" define a "real world" context of use. An assay that measures the presence of a material, which has a stated correlation to a predisposition to the onset of a particular disease condition, would also define a "real world" context of use in identifying potential candidates for preventive measures or further monitoring. On the other hand, the following are examples of situations that require or constitute carrying out further research to identify or

reasonably confirm a "real world" context of use and, therefore, do not define "substantial utilities":

A. Basic research such as studying the properties of the claimed product itself or the mechanisms in which the material is involved.

B. A method of treating an unspecified disease or condition. (Note, this is in contrast to the general rule that treatments of specific diseases or conditions meet the criteria of 35 U.S.C. 101.)

C. A Method of assaying for or identifying a material that itself has no "specific and/or substantial utility".

D. A method of making a material that itself has no specific, substantial, and credible utility.

E. A claim to an intermediate product for use in making a final product that has no specific, substantial, and credible utility.

See also the MPEP § 2107 - 2107.02.

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 23,24,26 and 28-33 are rejected under 35 U.S.C. 101 because the claimed invention lacks patentable utility. The rejection set forth on pages 2-6 of the previous office action mailed 09/15/2004 is maintained for claims 23,24 and 26 and is applied to newly added claims 28-33 as set froth below.

The instant specification has discussed that the mice of the instant invention can be used as models of disease to screen for drug therapies and as a tool for studying the function of a TRP6 gene. As set forth in the previous office action, these uses fail to meet the standards of a specific, substantial and well-established utility required under 35 U.S.C. 101: In summary,

the utilities provided by Applicant for the claimed mouse are not specific or substantial and therefore are not well established because the use of the mouse in screening for drugs to treat an unknown disease is not specific. The use for the claimed mouse in characterizing the function of TRP6 gene is not substantial. The basis for this rejection is further set forth in the previous office action and in the guidelines above.

Applicant has argued that the Patent Office guidelines state that a rejection for lack of utility may not be imposed where an invention has a well-established utility or is useful for any particular practical purpose. Applicant cites excerpts from an NIH website, Austin et al., 2004, Lewin's Genes VII, and others (pages 5-9 of Applicant's response) in establishing that knockout mice are invaluable tools of scientific research. Applicant also cites the MPEP in discussing the utility of research tools (pages 8-9 of Applicant's response; MPEP 2107.01, I). In general, Applicant does not understand how the invention cannot have utility when the invention is being used by one of skill in the art and has clearly been accepted as useful by several leaders in the field of transgenic technology.

In response, the instant invention has failed to meet the requirements of possessing a well-established utility and for a use with any particular practical purpose. A well-established utility and a utility with a particular practical purpose is one that is specific and substantial (see MPEP 2107(II)(A)(3)(ii) and MPEP 2107 (II)(B)(1)). The utility of the instant invention is neither specific nor substantial for reasons of record. Applicant is reminded that the utility guidelines (see above) expressly state that utilities requiring further research to identify or reasonably confirm a use do not define substantial utilities. Examples of uses that are not considered substantial utilities include basic research in studying the claimed product and use to

screen for therapeutics for an unspecified disease. The use of the invention by the skilled artisan does not impart patentability or patentable use on the invention for reasons set forth above.

With specific respect to Applicant's applied references, the validity of the opinion of the NIH, Ben Lewin and Austin et al. with respect to the value of the knockout mouse in determining gene function is not questioned. However, the use of a mouse to determine gene function, as set forth above, does not meet the requirement that a utility be specific and substantial, and therefore, does not fulfill the requirements of utility under 35 USC 101. With respect to MPEP 2107.01, I, a gas chromatograph is a research tool with a well-defined function and highly specific use that does not necessitate further study of itself. It may be that a gas chromatograph may be used for a wide variety of analyses; however, this does not change its specific use for analyzing a sample. In contrast, the claimed invention is not a general tool for analyzing other samples and, at most, serves to study the function of a single gene. In this respect, the utility of a knockout mouse cannot be compared to a gas chromatograph. Therefore, the utility of the instant invention is neither specific nor substantial.

Applicant also discloses the commercial use of the claimed mice and states that commercial use and acceptance is one important indication that the utility of an invention has been recognized by one of skill in the art (page 10 of Applicant's remarks). Applicant asserts that the claimed mice have been sold to at least 4 commercial entities.

In response, Applicant fails to provide description or evidence of such commercial use. Applicant has not provided any evidence pertaining to what the mice are being used for and therefore, without evidence to the contrary, it is assumed that the mice are being used for the

uses of record, namely in screening for drugs to treat a non-specified disease, in studying gene function and in studying gene expression (see below). As set forth above and in the previous office action, theses uses are not specific or substantial. Applicant is reminded that the requirements under §101 and §112, 1st para. must be met at the time the application is filed. The discovery of a use meeting these requirements after the application is filed does not satisfy the statutory requirements under either §101 or §112, 1st para. See *In re Kirk*, 153 USPQ 48, 52 (CCPA 1967); *In re Wright*, 27 USPQ2d 1510, 1514 (Fed. Cir. 1993).

Applicant has referred to the principles set forth in *In re Brana* (see pages 8-10 of Applicant's remarks). Applicant asserts that the specification supports a use of the knockout mouse that is specific and substantial in light of the teaching of *In re Brana*.

In response, the fact pattern in *Brana* does not correlate to the fact pattern of the instant application. In *Brana*, the court addressed two separate issues, utility and enablement. The court held that the specification did, in fact, disclose a specific and substantial use for the compound, treating leukemia, and that this use was overlooked by the PTO in making the rejection under 101. The court observed that the claimed compound was similar in structure to compounds in the prior art that were useful in treating leukemia. The claimed compound behaved in a manner similar to that of the prior art in art accepted assays for anti-leukemic activity. Therefore, the specification enabled the use. The instant specification and the art of record fail to support such a patentable utility for the instant invention and therefore, the principles set forth in *In re Brana* do not apply to the instant invention.

Applicant has stated that the mice are useful for studying expression of a TRP6 gene because the mice contain a lacZ reporter gene (page 15 of Applicant's response). Claim 23 has

been amended to recite that the mouse contains a null allele that comprises exogenous DNA comprising a gene encoding a visible marker that is capable of expression in the brain. Claim 33 recites that the visible marker is lacZ.

In response, this is only a general utility of further research that applies to any knockout mouse and is not specific. It is a widely used technique to generate mouse knockouts by inserting a visible reporter gene into an endogenous gene. Moreover, beyond only providing an expression pattern in the mouse as a whole, the specification fails to teach why or how to study any of these observed expressions in particular in the thalamus as instantly claimed. The specification fails to provide any specific utility for the claimed product. Just as any gene can be cloned to study gene expression, any gene can be knocked out to study function and/or expression. Furthermore, the claims are drawn to the mouse wherein the marker gene is capable of expression in the brain. The specification teaches in Example 3, that the lacZ expression is expressed in the brain, lung, bone marrow and reproductive system (page 53, lines 4-8). Applicant claims a mouse wherein the reporter is only expressed in the brain. It is not known how the skilled artisan would use the mouse with expression in the brain as opposed to the other expression domains because the specification does not set forth any characteristic or quality of the mouse that would establish that this particular domain makes the mouse useful.

With respect to the aspect of the rejection pertaining to the claimed phenotype of increased pain threshold, Applicant argues that one skilled in the art would clearly recognize the significance of a transgenic mouse having increase pain threshold. Applicant reasons that if disruption of the gene causes increased pain, then antagonism of the gene expression product

would be expected to have a similar effect in reducing pain as exampled by claim 34.

Applicant argues that wild-type control mice were used and that the observed phenotypes could clearly be attributed to the mutation. In response to the rejection asserting that there is no evidence that TRP6 has a role in pain, Applicant asserts "that now there is" (page 13, final 3 paragraphs). Applicant is reminded that the arguments of counsel cannot take the place of evidence in the record. In re Schulze, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); In re Geisler, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness."). Applicant argues that the Federal Circuit has set forth that the specification must be taken as in compliance with the enablement requirement unless there is reason to doubt the objective truth (page 14, paragraph 2). Applicant has argued that definitive correlation is not necessary.

In response, no evidence has been supplied to support that TRP6 has any role in pain. Applicant's argument that there now is such evidence is not persuasive. Furthermore, without knowing the role of TRP6, it cannot be concluded that the performance of the claimed mouse in a single behavioral test indicates that the mouse has a pain or nociceptive abnormality. The phenotype caused by the deficiency, at best, causes an altered response to the hot plate test. Correlation to altered nociception is not supported. The cause of the altered response in the hot plate test cannot be determined based on the evidence record. TRP6 is an uncharacterized ion channel. There is no evidence that it plays a role in nociception at all. As set forth on page 4 of the previous office action, the altered response on the hot plate test could just as well be indicative of a slower neurological response that has nothing to do with nociception. Without

some further characterization of the mouse or of the TRP6 gene, the person of ordinary skill in the art would have to perform additional experimentation to either obtain this support or to know how to use a phenotypic modulator such as that identified through methods of using the claimed animal as set forth by claim 34.

In light of the above, the skilled artisan would not find the asserted utility of the transgenic mouse and cells encompassed by the claims to be specific and substantial.

Enablement

Claims 23,24,26 and 28-33 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well-established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention. New grounds of rejection under the enablement requirement based on newly added claims and claim amendments are set forth below.

1) The breadth of claims 23,26,28,29 and 31-33 encompasses transgenic mice comprising a disruption in the TRP6 gene wherein the mice fail to exhibit any particular phenotype as the claims fail to recite a specific phenotype. Claims 23,26,28 and 31-33 encompass mice heterozygous for the disruption and claims 23,26,29 and 31-33 encompass mice homozygous for the disruption.

Applicant has amended the claims removing phenotypic limitations and adding the limitation that the gene disruption is a null allele. Such a limitation is not sufficient to overcome the requirement for a phenotypic limitation in light of the unpredictability of phenotype in knockout mice (see pages 9-10 of the office action mailed 04/06/2004) and the

lack of support for the described disruption being a null. The specification does not provide any evidence such as RT-PCR or structural analysis of the gene product that supports a total loss of gene function. Gene disruptions can create hypermorphic, hypomorphic, dominant negative and null alleles. The specification does not teach what type of allele is created by the disruption taught in the specification. Therefore, unless Applicant can point out support for the described disruption resulting in a null allele, the specification does not enable making the claimed mouse wherein the genome of the mouse comprises a null TRP6 allele and therefore a phenotypic limitation is required to overcome the unpredictability of phenotype inherent in the art of making transgenic mice.

The claims are also not enabled with respect to use the mice as broadly claimed. The mice encompassed by the claims appear to fail to differ from wild-type. Without a phenotype for the mice, the skilled artisan would not know how to use them. It would require undue experimentation for the skilled artisan to determine how to use the mice lacking a phenotype as encompassed by the claims.

2) The claims as written also encompass transgenic mice whose genome comprises a transgene construct comprising a null TRP6 allele wherein the TRP6 allele is not an endogenous allele but is encoded by a transgene comprising a separate promoter that is inserted into the genome of the animal. The specification is enabling only for insertion of a gene disruption into the endogenous TRP6 gene. The specification does not teach insertion of a null TRP6 transgene and does not teach the phenotypic effects of such an insertion. In light of the unpredictability of phenotype in transgenic mice and in light of the lack of support in the

specification with respect to such a gene insertion, it would require undue experimentation to determine how to use the mice broadly encompassed by the claim.

Therefore, in light of the breadth of the claims, the lack of guidance in the specification and the unpredictability in the art of knockout mice, the skilled artisan would have to perform undue experimentation to determine how to make and use the claimed mice.

Written Description

Claims 23,24,26 and 28-33 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116).

1) The specification has described a nucleotide sequence, encoding a TRP6 receptor as set forth by SEQ ID NO:1. In the instant case the genus of TRP6 genes encompassed by the claims lack a written description. The claims broadly encompass any TRP6 gene, including heterologous TRP6 genes. The specification fails to describe what DNA molecules other than the nucleotide sequence set forth in SEQ ID NO:1 fall into this genus and it was unknown as of

Applicants' effective filing date that any of these DNA molecules would have the property of encoding a TRP6 polypeptide having the same structural and functional properties as that encoded by genomic sequence that correlates to the cDNA sequence of SEQ ID NO:1. There is no evidence on the record of a relationship between the structures of the nucleotide sequences coding for a mouse TRP6 receptor gene product and the nucleotide sequence set forth by SEQ ID NO:1 that would provide any reliable information about the structure of DNA molecules within the genus. The claimed invention as a whole is not adequately described if the claims require essential or critical elements that are not adequately described in the specification and that is not conventional in the art as of applicants effective filing date. Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641,1646 (1998).

With the exception of the sequence referred to above, the skilled artisan cannot envision the detailed chemical structure of the encompassed polynucleotides, and therefore conception is not achieved until reduction to practice has occurred regardless of the complexity or simplicity of the method of isolation. The skilled artisan cannot envision the detailed chemical structure of the encompassed nucleic acid molecules and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The nucleic acid itself is

required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

In view of the above considerations one of skill in the art would not recognize that applicant was in possession of the necessary common features or attributes possessed by any member of the genus of genes encoding a TRP6 gene product other than that set forth by SEQ ID NO:1. Therefore, only the genomic TRP6 gene encoding the same gene product as the cDNA set forth by SEQ ID NO:1, but not the full breadth of the claims meet the written description provision of 35 U.S.C. §112, first paragraph. University of California v. Eli Lilly and Co., 43 USPQ2d 1398, 1404, 1405 held that "to fulfill the written description requirement, a patent specification must describe an invention and do so in sufficient detail that one skilled in the art can clearly conclude that "the inventor invented the claimed invention".

2) The claims as written also encompass transgenic mice whose genome comprises a transgene construct comprising a null TRP6 allele wherein the TRP6 allele is not an endogenous allele but is encoded by a transgene comprising a separate promoter that is inserted into the genome of the animal. The specification describes only the insertion of a gene disruption into the endogenous TRP6 gene. The specification does not describe insertion of a null TRP6 transgene and does not describe the resulting mouse such that the phenotypic effects of such an insertion is known. Therefore, one of skill in the art would not recognize that

applicant was in possession of the mouse whose genome comprises a transgene encoding a null TRP6 allele as encompassed by the claims.

Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (see page 1115).

New Matter

Claims 2-4,6-9,13 and 32-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application".

Claim 23 has been amended to recite that the mouse contains a null allele that comprises exogenous DNA comprising a gene encoding a visible marker that is capable of expression in the brain. Claim 34 recites that the visible marker is lacZ. Applicant points to the specification for support of these amendments at page 8, lines 4-8; page 19, line 18-page 20, line 21; Example 2; the Figures; and the original claims to provide support for these amendments. Page 8, lines 4-8 defines the term “transgenic animal”. Example 2 describes the expression of a lacZ reporter gene.

The specification does not describe a genus of knockout mice wherein the targeting construct contains a generic “visible marker”, particularly where the exogenous DNA need not

contain a positive selection marker. The specification teaches that the targeting construct contains a positive selection marker between the targeting sequences, which is not a limitation recited by the claims. Since the claims are now limited specifically to a null allele comprising exogenous DNA, omission of the positive selection marker is new matter, i.e. the specification fails to disclose embodiments where the exogenous gene does not encode a positive selection marker. Furthermore, the specification shows that the lacZ gene was the only screenable marker contemplated and lacZ is not a visible marker, per se. lacZ is a gene that encodes a product, β-galactosidase, the presence of which can be visualized indirectly through an assay that results in enzymatic production of a colored visible product. It is the product of the reaction that is visible, not the lacZ or the β-galactosidase. With respect to the visible marker, the specification does not mention, even in passing, a general feature of the claimed invention where the exogenous DNA encodes a visible marker, consequently, recitation of the limitation of "visible marker" in the current context is new matter. Applicant has not contemplated use of a visible marker. Furthermore, if lacZ were considered to be a visible marker, disclosure of a single species is rarely, if ever, sufficient to describe a broad genus, particularly when the specification fails to describe the features of that genus, even in passing. See, for example, *In re Shokal*, 113 USPQ 283 (CCPA 1957); *Purdue Pharma L.P. v. Faulding Inc.*, 56 USPQ2d 1481 (CAFC 2000).

To the extent that the claimed compositions and/or methods are not described in the instant disclosure, claims 84-90 are also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to

make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

MPEP 2163.06 notes "If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981)." MPEP 2163.02 teaches that "Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed. If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application. MPEP 2163.06 further notes "When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure" (emphasis added).

Claim Rejections - 35 USC § 112-2nd paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 23,24,26 and 28-33 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 23 is unclear because the claim recites that the marker is capable of expression. It is unclear whether these characteristics actually occur or that the marker could potentially do these described things. "Capable of" implies a property , however, the claim fails to set forth ant specific ctructural or functional limitation that provides this property. Therefore, it is unclear if the latent property is ever obtained. Claims 24,26 and 28-33 depend from claim 23.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

1) Claims 23,26,28,29 and 31-33 are rejected under 35 U.S.C. 103(a) as being unpatentable over Mansour (*Development*, 1993, vol. 117, pp 13-28) in view of Genbank Accession No. U49069 (March 1998).

Mansour taught transforming a mouse ES cell with a nucleic acid construct targeting the int-2 gene, resulting in an inactivating (null; see abstract and page 23, paragraph 3) insertion of a selective marker gene into the endogenous int-2 locus (page 14, col. 1, paragraph 3), and using said cell to generate a mouse whose genome comprises a disruption in the int-2 gene (for specific method steps see page 15, col. 2, paragraph 3). The targeting construct comprised both a neo resistance gene and a visible lacZ marker (page 14, col. 1, paragraph 3). Mansour differs from the claimed invention in that the targeting construct does not disrupt the TRP6 gene.

However, at the time the claimed invention was made, Genbank Accession No. U49069 taught the cloning of the mouse TRP6 cDNA.

Accordingly, it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made, to make cells and a knockout mouse having a disruption in a targeted gene as taught by Mansour wherein the gene was TRP6 as taught by Genbank Accession No. U49069. One of ordinary skill in the art would have been sufficiently motivated to replace the int-2 gene with the TRP6 gene, as it was an art-recognized goal to determine the physiological role of a gene of interest by the generation of a knockout mouse. One of ordinary skill in the art would have been sufficiently motivated to disrupt the TRP6 gene to determine its role in relation to other genes and in signal transduction, as described by Genbank Accession No. U49069.

Note that absent any phenotypic requirements for the claimed transgenic mouse, the combination of the cited prior art is sufficient to make obvious the claimed invention. Mansour discloses the applicability of gene targeting to many other genes so that a correlation can be drawn between the malfunctioning gene and the manifestation of disease (page 41, column 2, 2nd full paragraph). The skilled artisan could expect to obtain the claimed mouse with a reasonable level of success because it was routine in the art to knock out genes and because the claims are so broad as to encompass any phenotype, any mouse obtained by the method would fulfill the limitations of the claims.

Thus, the claimed invention is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ram Shukla can be reached on (571) 272-0735. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Valarie Bertoglio
Examiner
Art Unit 1632